JACC Vol. 33, No. 1
January 1999:206–11

Prognosis of Completely Asymptomatic Adult Patients With Hypertrophic Cardiomyopathy

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Objectives. **We investigated the long-term prognosis of completely asymptomatic adult patients with hypertrophic cardiomyopathy (HC). Diagnosis of HC was suspected because of an abnormal electrocardiogram and/or cardiac murmur and confirmed by echocardiography and/or left ventricular angiography, and hemodynamic investigation.**

Background. **Hypertrophic cardiomyopathy shows marked heterogeneity in clinical expression and prognosis. The prognosis of asymptomatic patients with HC has not been fully defined.**

Methods. **Of 128 consecutive adult patients with HC, 58 asymptomatic patients (Group 1, mean age 42.8 years) and 70 symptomatic patients (Group 2, mean age 50.4 years) were studied to assess cardiac mortality. Mean follow-up periods were 11.0 years for Group 1 and 9.1 years for Group 2.**

Results. **At presentation, Group 1 patients were younger and had smaller left atrial dimensions than did Group 2 patients. The annual cardiac mortality rate and the rate for sudden death alone in Group 1 were significantly lower than in Group 2 (0.9% vs. 1.9%, $p < 0.05$, 0.1% vs. 1.4%, $p < 0.05$, respectively). Although about one-third of the survivors in Group 1 had cardiac symptoms at their most recent evaluation, only one patient died suddenly compared with eight in Group 2. The annual mortality rate due to heart failure was similar in each group. Only a syncopal episode was associated with both cardiac death and sudden death for both groups combined.**

Conclusions. **The cardiac mortality rate for completely asymptomatic adult patients with HC was very low, significantly lower than that of symptomatic patients, and there was a disproportionately low incidence of sudden death.**

(J Am Coll Cardiol 1999;33:206–11)

Earlier hospital-based clinical investigations of hypertrophic cardiomyopathy (HC) reported a high incidence of serious ventricular arrhythmias, sudden death, and overall annual mortality rates between 2% and 4% (1–11). In contrast, recent outpatient population or community-based studies have reported a favorable clinical course and prognosis (12–16). The diversity of clinical expression and prognosis in HC have become well known. It is, therefore, necessary to recognize all subsets of patients within the broad disease spectrum of HC for a more realistic clinical perspective.

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Although some patients with HC may be severely symptomatic or require surgical treatment (17–19), many remain asymptomatic and unaware of their disease for years. In such patients, the diagnosis of HC is often first made in the course of routine examinations, and their disease process and long-term outcomes are not well defined. Consequently, we investigated the clinical features and long-term outcomes in a relatively large group of adult patients who had HC but no cardiac symptoms. They were all diagnosed because of an abnormal electrocardiogram (ECG) and/or cardiac murmur identified at the time of routine health examinations or during evaluation of noncardiac problems.

Methods

Selection of patients. In Japan, annual health examinations of students and workers, including an ECG, are part of the health care system. In addition, the ECG is often used as a routine screening test for patients with symptoms not necessarily limited to cardiac symptoms to exclude cardiovascular abnormalities. A considerable number of asymptomatic patients with HC are therefore identified initially at local general hospitals owing to a cardiac murmur or an abnormal ECG. Because of our interest in HC, we have vigorously evaluated patients with HC using cardiac catheterization for accurate diagnosis and further investigations, and have followed even asymptomatic patients meticulously. The vast majority of our patients have been specifically referred from outlying hospitals with an established diagnosis of HC for cardiac catheterization, advice, and advanced care because of the known interest of our institution in HC.

One hundred and fifty-two patients with HC were admitted to our institution for cardiac catheterization from August 1968

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Manuscript received April 21, 1998; revised manuscript received August 5, 1998; accepted September 15, 1998.

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0735-1097/99/$20.00
PII S0735-1097(98)00555-5

Abbreviations and Acronyms

ECG = electrocardiogram
HC = hypertrophic cardiomyopathy
LA = left atrium
LV = left ventricle
NYHA = New York Heart Association

to May 1994. Eighteen patients were excluded because of 1) young age (<20 years) at diagnosis (n = 3); 2) severe mitral regurgitation associated with ruptured mitral valve chordae (n = 1); 3) coronary artery disease with stenosis ≥75% in major coronary arteries on coronary angiography (n = 4); or 4) apical hypertrophy (n = 10). Apical hypertrophy was defined as the presence of a spadelike configuration of the left ventricle (LV) at diastole demonstrated by LV angiography, with a septal thickness ≤15 mm by echocardiography and/or LV angiography (20). Only six patients (3.9%) were lost to follow-up. Thus, the final study cohort consisted of 128 adult patients with HC.

All patients were followed until death or for a minimum of 1 year. The mean follow-up time was 9.9 years (range 5 months to 27 years). There were 112 men and 16 women aged 20 to 74 years (mean 47 years). Of the 128 patients with HC, 58 completely asymptomatic patients (Group 1) were identified and represent the focus of the present study. The remaining 70 patients (Group 2) had at least one of the following cardiac symptoms: cardiovascular functional limitation (New York Heart Association [NYHA] functional class ≥II) (n = 27), chest pain (n = 19), palpitations (n = 19), or a syncopal episode <1 year before presentation (n = 8). None of the patients were in NYHA functional class IV. None were included solely on the basis of a diagnosis made during a systematic pedigree analysis. Of the 128 patients, 124 were from separate pedigrees and completely unrelated. The remaining four patients were from two families, both of which contributed two patients to the cohort.

The diagnosis of HC was based on echocardiographic and LV angiographic identification of a hypertrophied, nondilated LV with normal systolic function (LV ejection fraction by LV angiography >0.5), and the absence of another cardiac or systemic disease capable of producing the magnitude of LV hypertrophy present in the patient (21,22). Because 10 patients were presented before echocardiography was introduced into our clinical practice in 1974, the diagnosis of HC was made from the clinical, ECG, hemodynamic, and angiographic findings (2,4,5,23). In seven of these patients the diagnosis was subsequently confirmed by echocardiography (22). Patients with a history of hypertension were included in the study. In the vast majority of cases, the hypertension was mild or well controlled with therapy, and was clearly disproportionate to the degree of LV hypertrophy observed by echocardiography.

Clinical examination. At the time of admission, clinical characteristics including age, family history of HC or sudden death, cardiac symptoms, and NYHA functional class were recorded. Physical examination, 12-lead ECG, and baseline laboratory studies were performed, including left and right cardiac catheterization, LV and coronary angiography, M-mode echocardiogram, 2-dimensional echocardiography, and 24-h Holter ECG when possible.

Cardiac catheterization. All patients underwent right and left heart catheterization and LV and coronary angiography. Hemodynamic data judged suitable for quantitative analysis were available in 118 (92%) patients. Patients were considered to have an LV outflow obstruction if the pressure gradients measured under basal conditions or with provocation (with isoproterenol infusion, premature ventricular contractions, or the Valsalva maneuver) were greater than 30 mm Hg. Cardiac output was determined by thermodilution. The LV ejection fractions were calculated from the cineangiograms by the area-length method (24). We received informed consent from all patients before cardiac catheterization.

Echocardiography. Echocardiographic studies were performed in 118 (92%) patients at presentation using commercially available instruments. Echocardiographic data judged suitable for quantitative analysis was available in 113 (88%) patients, and the following measurements were recorded for each patient: diastolic ventricular septal and posterior wall thickness, indexed LV cavity dimensions during systole and diastole, and indexed left atrial (LA) dimensions (25).

Electrocardiography. The 12-lead ECG recorded at presentation was evaluated for rhythm disturbances and conduction disease including atrioventricular block and intraventricular conduction delay. The Sokolow-Lyon index was used as a measure of LV hypertrophy (26). A 24-h Holter ECG was obtained in 84 (66%) patients in similar proportions in both groups. Supraventricular or ventricular tachycardia was defined as three or more premature complexes in succession.

Medications. In the present study, patients were generally given medical therapy in a systematic and consistent fashion. Medical therapy was directed toward control of symptoms, arrhythmias, outflow obstruction, coexisting hypertension, and prevention of peripheral embolization. Patients with angina pectoris were treated with beta-adrenergic blocking agents (usually propranolol, 30 to 120 mg/day) if obstruction was present, or with calcium channel blockers (usually verapamil, 120 to 240 mg/day) if absent. Patients with severe congestive symptoms received diuretic agents (e.g., furosemide, thiazides) or an angiotensin-converting enzyme inhibitor (captopril) if obstruction was absent. None received amiodarone. Group 1 patients did not receive drug treatment unless there was coexisting hypertension, cardiac symptoms developing during the follow-up period, or additional clinical variables regarded as risk factors of unexpected sudden death, such as an unfavorable family history or the presence of ventricular tachycardia. Some Group 2 patients did not receive treatment because they exhibited only mild symptoms, showed poor compliance, or their condition improved during the follow-up period. Because of the long time span of the study and the relatively rare occurrence of HC, randomization was not performed. As few patients were severely symptomatic with poor response to

medical therapy, no myectomies for the surgical relief of obstruction were performed.

Follow-up. Initial clinical presentation was defined as the time when the diagnostic cardiac catheterization was performed at our institution. The most recent clinical assessments were obtained during May 1995. Clinical details and follow-up were obtained by reviewing each subject's complete (inpatient and outpatient) medical records and mail contact, or by telephone contact when necessary. However, reliable information regarding the HC-related symptoms at the most recent clinical evaluation was not available for all the patients who died in each group as well as for 1 survivor in Group 2 who experienced a cerebral vascular accident. In cases of death, the cause was obtained from the death certificate, autopsy when available, or by questioning the relatives or physicians involved in the patient's care. Cardiac death was defined as sudden death or congestive heart failure death. Sudden death was assumed to be cardiac, and was defined as a witnessed death within 1 h after the onset of symptoms or an unwitnessed death in a subject known to be alive and functioning normally 24 h before death (27). Unexpected cardiovascular collapse occurring unexpectedly in the context of severe congestive heart failure was regarded as heart failure death rather than as sudden death.

Statistical analysis. Data were expressed as mean ± SD. Statistical analyses were performed on a Macintosh LC 630 computer using the Stat View 4.11 application package and the Survival Tool 1.11 plug-in application. Differences between continuous variables were determined using the unpaired *t* test. Differences between proportions were determined using the chi-square test or the Fisher exact test, as appropriate. The annual mortality rate was calculated according to the Kaplan-Meier method (28). Comparison of survival curves between Group 1 and Group 2 was made using the log-rank test. To assess the risk factors for cardiac death and for sudden death, univariate analysis was performed using the Cox regression model for both groups combined.

Results

Baseline clinical characteristics. In all the Group 1 patients, the initial reason for diagnosis of HC was an abnormal ECG and/or cardiac murmur. These were identified during evaluation of noncardiac problems in approximately one-half of the patients (n = 30), and at the time of a routine health examination in the other half (n = 28). In contrast, most of the Group 2 patients were diagnosed because of cardiac symptoms (n = 60). The remaining 10 patients were diagnosed because of an abnormal ECG and/or cardiac murmur identified at the time of a routine health examination (n = 6) or during evaluation of noncardiac problems (n = 4).

Group 1 patients were younger ($p < 0.01$) and showed a higher percentage of men ($p < 0.05$) than did Group 2. There were similar frequencies of patients with coexisting hypertension and of patients with a family history of HC or sudden death in each group. Table 1 gives details on baseline clinical features.

Group 2 had significantly larger indexed LA dimensions ($p < 0.05$) than did Group 1; ECG, hemodynamic, and 24-h Holter ECG data were similar in each group. There was no sustained (>30 s) ventricular tachycardia in either group. Table 2 provides more ECG, hemodynamic, echocardiographic, and 24-h Holter ECG data.

Table 1. Comparison of Clinical Features at Presentation Between Patients in Group 1 and in Group 2

	Group 1 (n = 58)	Group 2 (n = 70)	p Value
Mean age (year)	42.8 ± 11.5	50.4 ± 10.8	$p < 0.01$
(Range)	(20–71)	(23–74)	
Mean follow-up period (year)	11.0 ± 5.9	9.1 ± 5.7	NS
Men (%)	95	81	$p < 0.05$
NYHA functional class			
I	58	43	—
II	0	17	—
III	0	10	—
IV	0	0	—
Cardiac symptoms			
Chest pain	0	19	—
Episode of syncope	0	8	—
Palpitations	0	19	—
Hypertension	17	27	NS
Family history of			
HC	9	5	NS
Sudden death	12	7	NS
Medical therapy*	35	53	NS

*Medical therapy with beta-blockers, calcium channel antagonists, or both for more than one-half of the follow-up period. Data are expressed as mean value ± SD or number of patients. ECG = electrocardiogram; HC = hypertrophic cardiomyopathy; NYHA = New York Heart Association.

Long-term follow-up. *Survival.* During follow-up, there were 3 cardiac deaths and 2 noncardiac deaths in Group 1, and 11 cardiac deaths and 6 noncardiac deaths in Group 2. Regarding the modes of cardiac death, only one patient in Group 1 died suddenly compared with eight in Group 2. Two patients in Group 1 died of congestive heart failure versus three in Group 2. The annual cardiac mortality rate was 0.9% in Group 1 and 1.9% in Group 2 (Fig. 1). The annual mortality rate confined to sudden death was only 0.1% in Group 1 and 1.4% in Group 2 (Fig. 2). The annual cardiac mortality rate and the rate for sudden death alone in Group 1 were significantly lower than in Group 2 ($p < 0.05$, $p < 0.05$, respectively). The annual mortality rate due to heart failure was similar in both groups.

Clinical, ECG, hemodynamic, echocardiographic, and 24-h Holter ECG variables were examined for an association with decreased survival during the follow-up period for both groups combined. Univariate analysis revealed that only a syncopal episode was associated with increased incidence of both cardiac death ($p < 0.01$) and sudden death ($p < 0.05$).

Symptoms. At the most recent evaluation of the 53 survivors in Group 1, 34 patients were still completely asymptomatic, and the remaining 19 patients (36%, or about one-third) had at least one newly developed cardiac symptom: cardiovascular functional limitation in 10, chest pain in 9, and palpita-

Table 2. Comparison of ECG, Hemodynamic, Echocardiographic and 24-h Holter ECG Data at Presentation Between Patients in Group 1 and in Group 2

	Group 1 (n = 58)	Group 2 (n = 70)	p Value
ECG data	(n = 58)	(n = 70)	
Atrial fibrillation	4	13	NS†
Established	1	1	
Paroxysmal	3	12	
Atrioventricular block	1	0	
Intraventricular conduction delay	4	5	NS
$SV_1 + RV_5$ (mV)	51.3 ± 23.1	52.3 ± 22.8	NS
Hemodynamic data	(n = 54)	(n = 64)	
PAWP (mm Hg)	8.3 ± 3.8	8.5 ± 4.1	NS
LVEDP (mm Hg)	14.3 ± 5.9	15.7 ± 6.5	NS
Left ventricular ejection fraction	0.72 ± 0.10	0.72 ± 0.09	NS
Stroke volume index (ml/m^2)	52 ± 12	51 ± 12	NS
Left ventricular outflow obstruction	14	17	NS
Echocardiographic data	(n = 52)	(n = 61)	
Left atrial dimension index (mm/m^2)	21.0 ± 3.8	22.7 ± 4.6	$p < 0.05$
Interventricular septal thickness (mm)	20.4 ± 5.1	20.6 ± 6.4	NS
Posterior wall thickness (mm)	12.9 ± 3.0	13.0 ± 2.8	NS
LVDdI (mm/m^2)	26.6 ± 4.1	26.7 ± 3.9	NS
LVDsI (mm/m^2)	16.2 ± 3.1	16.1 ± 3.5	NS
24-h Holter ECG data	(n = 38)	(n = 46)	
Ventricular tachycardia	6	4	NS
PSVT	4	11	NS

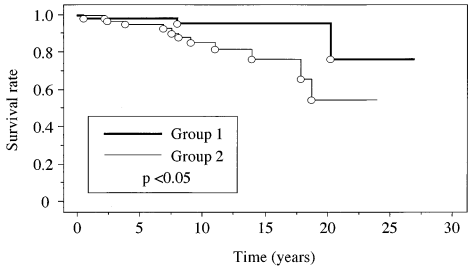
†Actual p value = 0.053. Data are expressed as mean value ± SD or number of patients. LVDdI = left ventricular end-diastolic cavity dimension index; LVDsI = left ventricular end-systolic cavity dimension index; LVEDP = left ventricular end-diastolic pressure; PAWP = pulmonary artery wedge pressure; PSVT = paroxysmal supraventricular tachycardia; other abbreviations as in Table 1.

tion in 12. Of the 53 survivors in Group 2, except for the aforementioned patient who had the cerebral vascular accident, 20 patients (38%) showed improvement after treatment and were completely asymptomatic. None of the patients in either group had newly developed syncopal episodes.

Discussion

To our knowledge, this study is the first to report a prognosis for a relatively large population of completely asymptomatic adult patients with HC during the long-term follow-up period. The cardiac mortality rate of asymptomatic

Figure 1. Comparison of survival rates from cardiac death between Groups 1 and 2.



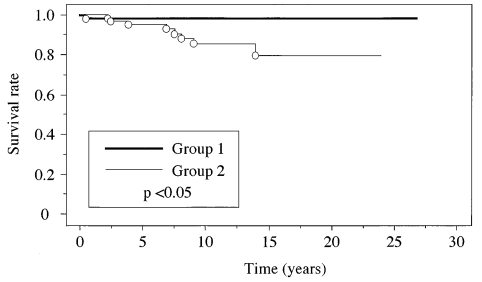


Figure 2. Comparison of survival rates from sudden death between Groups 1 and 2.

patients (Group 1) was very low, significantly lower than that of symptomatic patients (Group 2), and there was a disproportionately low incidence of sudden death.

Our asymptomatic patient group within the broad clinical spectrum of HC. Despite numerous clinical investigations of HC, the natural history of this disease has not been fully defined, primarily because of substantial diversity with respect to clinical presentation and prognosis. Our study is important to asymptomatic patients who, owing to the absence of symptoms, are not likely to seek medical care. The aforementioned distinct health care system, the clinical practice in Japan, and our own policy for the management of patients with HC afforded us the opportunity to investigate the clinical course and long-term prognosis of this unique spectrum of HC. We employed strict criteria for identifying Group 1 patients: only those with no cardiac symptoms were included. Initial diagnosis of HC in Group 1 was suspected because of abnormal ECGs and/or cardiac murmurs. We believe our asymptomatic patient group is at the mild end of the disease spectrum for which widely published data on HC are lacking.

Comparison with previous studies. Most prior clinical studies on the natural history of HC have been based on populations of highly selected patients from large tertiary referral centers and have reported a poor prognosis due largely to unexpected sudden cardiac death (3,5–7,29). The cardiac mortality rates (approximately 2%) and the modes of death observed in Group 2 were almost consistent with those in the prior reports. However, Group 1 patients showed a benign clinical course. Other recent clinical investigations on populations, which seem to present a benign HC spectrum, also reported a favorable prognosis. Shapiro and Zezulka (13) studied 39 patients over a 5-year period at a general hospital and showed that mortality rates among these patients did not differ from normal. Spirito et al. (12) followed 25 outpatients for an average of 4 years and found no cases of cardiac death. Kofflard et al. (14) followed a large clinic population of 113 patients for an average of 7 years and showed an annual cardiac mortality rate of only 1%.

Indeed, these study populations seem to represent a relatively mild disease spectrum compared with the referral hospital-based populations in the prior studies. However, they still provide few details concerning the asymptomatic patients with HC. Hecht et al. (30) studied a subgroup of 31 middle-

aged asymptomatic patients with HC and followed them for an average of 7 years. There were four sudden deaths, and these investigators concluded that their asymptomatic patients remained at enhanced risk of sudden death later in life. However, because their asymptomatic patients were defined only by the absence of functional limitation (NYHA functional class I), these patients seemed not to be completely asymptomatic by our strict definition, and so would differ from our Group 1 patients.

Reasons for the benign prognosis observed in Group 1. The infrequency of sudden cardiac death clearly contributed to the favorable prognosis in our asymptomatic Group 1 patients, and there are several possible explanations for these findings. The major risk factors for sudden death in patients with HC have been suggested to be clinical and arrhythmia-related (3,5,8,10,31,32). These risk factors include younger age at diagnosis (<14 years) (3,5), a family history of sudden death due to HC (3,10,31), and a history of syncope (3,8,32). Our study patients were confined to adult patients diagnosed with HC at age ≥20 years, and did not include children who were known to be at enhanced risk of sudden death without known medical problems or symptoms (5,31). We also found that a history of syncope was a major risk factor for sudden death and had the most important impact on cardiac mortality. Regarding a family history of sudden death due to HC, however, we could not obtain reliable enough data to examine the relation between such a family history and subsequent cardiac mortality in this retrospective study. Thus, the benign prognosis in Group 1 seemed to result from our patient age and the absence of syncopal episodes.

Differences in clinical presentation between Groups 1 and 2. Group 2 patients were older and had larger LA dimensions than did Group 1. The LV diastolic function is well known to be impaired with aging (33,34). Symptomatic Group 2 patients appeared to have more impaired LV diastolic function affected by aging. Furthermore, it is expected that the more impaired LV diastolic function would be reflected in higher LA pressures, resulting in LA enlargement.

There were fewer females in Group 1 than in Group 2, and there was an apparent predominance of males in the entire study population, although HC is, in general, only a little more common in men (12,14). This discrepancy may be partly due to our patient selection process, which is affected by the health care system and by clinical practice in Japan. Because the labor participation rate of females is much lower than that of males in Japan, females are less likely to undergo company-sponsored health examinations that allow identification of the asymptomatic patients with HC.

Study limitations. There were also few younger patients (age at diagnosis <20 years) to allow us to investigate a patient population with a broad age range. Consequently, our observations should be interpreted with caution as they apply to a largely adult study cohort with male predominance, as described above.

Conclusions. In the present study, the cardiac mortality rate of completely asymptomatic adult patients with HC was very low, significantly lower than that of symptomatic patients, and there was a disproportionately low incidence of sudden death. Our findings may be useful in the management of patients with HC surveyed in routine examinations, and helpful in the investigation of the natural history of HC covering a broad clinical spectrum.

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